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Health Effects Assessment for Trichloroethylene

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16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with trichloroethylene. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to May, 1987. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. Ambient Water Quality Criteria for Trichloroethylene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-077. NTIS PB 81-117871.

U.S. EPA. 1981. The Carcinogen Assessment Group's Carcinogen Assessment of Trichloroethylene. Prepared by the Office of Health and Environmental Assessment, Carcinogen Assessment Group, Washington, DC. Internal draft.

U.S. EPA. 1982. Hazard Profile for Trichloroethylene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste, Washington, DC.

U.S. EPA. 1983. Review of Toxicological Data in Support of Evaluation for Carcinogenic Potential of Trichloroethylene. Prepared by the Office of Health and Environmental Assessment, Carcinogen Assessment Group, Washington, DC for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1985. Health Assessment Document for Trichloroethylene. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA 600/8-82-006F. NTIS PB 84-162882.

U.S. EPA. 1987. Integrated Risk Information System (IRIS). Risk Estimate for Carcinogens for Trichloroethylene. On line. (Preparation date: 2/18/87). Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

The intent in these assessments is to suggest acceptable exposure levels for noncarcinogens and risk cancer potency estimates for carcinogens whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard or risk associated with exposure to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for RfD_S estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980b) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_O) or inhalation (RfD_I) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1984).

For compounds for which there is sufficient evidence of carcinogenicity RfD_S and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980b). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. For carcinogens, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

Two oral bioassays have yielded positive results. In these studies, exposed mice showed an increased incidence of hepatocellular carcinoma. Using the geometric mean of the slope estimates from these studies, a carcinogenic potency of 1.1×10^{-2} $(mg/kg/day)^{-1}$ has been computed.

Trichloroethylene has been shown to be carcinogenic in mice by inhalation exposure in three strains and in rats in one experiment. Human epidemiological studies are inadequate to assess the potential carcinogenicity of trichloroethylene in humans.

U.S. EPA (1987b) used mouse data based on the incidence of lung tumors and the corresponding metabolized dose from the mouse inhalation studies to estimate a unit risk for inhalation exposure. Data concerning the pharmacokinetics of trichloroethylene in animals and humans was utilized to estimate effective dose levels. The resulting unit risk was 1.7×10^{-6} $(\mu g/m^3)^{-1}$. Trichloroethylene has been classified as a B2 carcinogen (U.S. EPA, 1987b).

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
CAS	Chemical Abstract Service
CS	Composite score
K_{oc}	Soil sorption coefficient
K_{ow}	Octanol/water partition coefficient
LOAEL	Lowest-observed-adverse-effect level
NOAEL	No-observed-adverse-effect level
ppm	Parts per million
RfD	Reference dose
RfD_I	Inhalation reference dose
RfD_O	Oral reference dose
RfD_S	Subchronic reference dose
RfD_{SI}	Subchronic inhalation reference dose
RfD_{SO}	Subchronic oral reference dose
SNARL	Suggested no-adverse-response level
STEL	Short-term exposure limit
TCA	Trichloroacetic acid
TCE	Trichloroethanol
TLV	Threshold limit value
TWA	Time-weighted average
v/v	Volume/volume

1. ENVIRONMENTAL CHEMISTRY AND FATE

The relevant physical and chemical properties and environmental fate of trichloroethylene (CAS No. 79-01-6) are as follows:

Chemical class:	halogenated aliphatic hydrocarbon (purgeable halocarbon)
Molecular weight:	131.4
Vapor pressure:	57.9 mm Hg at 20°C (Callahan et al., 1979)
Water solubility:	1100 mg/ℓ at 20°C (Callahan et al., 1979)
Log K_{ow}:	2.42 (Hansch and Leo, 1985)
Soil mobility: (predicted as retardation factor for soil depth of 140 cm and organic carbon content of 0.087%)	1.6 (Wilson et al., 1981)
K_{oc}:	87-150 (NLM, 1987)
BCF:	17 (in bluegill, Lepomis macrochirus) (U.S. EPA, 1980a)
Half-lives in	
Air:	4-5 days (U.S. EPA, 1982; NLM, 1987)
Water:	1-4 days (river) (Zoeteman et al., 1980) 30-90 days (lake) (Zoeteman et al., 1980)

The primary removal mechanism for trichloroethylene in the atmosphere is reaction with photochemically generated hydroxyl radicals. Products of this reaction are phosgene, dichloroacetyl chloride and formyl chloride. In photochemical smog situations, trichloroethylene degrades rapidly with a half-life on the order of hours (NLM, 1987).

The primary removal mechanism for trichloroethylene in water is expected to be volatilization. Bioaccumulation in aquatic organisms and adsorption to suspended solids and sediments are not expected to be important fate processes (NLM, 1987).

The half-life of trichloroethylene in soil was not located in the available literature. Trichloroethylene is expected to volatilize rapidly from soil surfaces. The half-life for evaporation from soil should be longer than its evaporation half-life from water (Wilson et al., 1981). In subsurface soil, no significant degradation is expected to occur under aerobic conditions, although some biodegradation may occur in anaerobic soils (HLM, 1987). Trichloroethylene is expected to be fairly mobile in soil as indicated by its K_{oc} and the retardation factor (velocity of water through soil divided by apparent velocity of the compound through soil). Undegraded residue is expected to leach into groundwater. Detection of this compound in a number of groundwater supplies supports this prediction (HLM, 1987).

2. ABSORPTION FACTORS IN HUMAN AND EXPERIMENTAL ANIMALS

2.1. ORAL

Rats and mice were given single 10, 500, 1000 or 2000 mg/kg doses of trichloro[^{14}C]ethylene in corn oil by gavage (Prout et al., 1984). Determination of radioactivity in the urine, feces, expired air and carcass after 24-72 hours showed that 92-100% of the doses were absorbed. Similar data were reported in an earlier study with rats (Daniel, 1963). Data are not available on the extent of gastrointestinal absorption of trichloroethylene by humans. See Section 4.3.2. for selected pharmacokinetic data.

2.2. INHALATION

In humans, absorption of trichloroethylene through the lungs is rapid, and complete tissue equilibrium is achieved after ~8 hours of exposure (U.S. EPA, 1985). See Section 4.3.2. for selected pharmacokinetic data.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Tucker et al. (1982) added trichloroethylene at four different dose levels to the drinking water of mice for 6 months (Table 3-1). The dose levels were calculated by measuring the concentration of trichloroethylene in the drinking water, and multiplying by the amount of water consumed by the animals each day. The amount of water consumed each day was estimated by measuring the water remaining in the drinking water bottles twice a week. Gas-liquid chromatography indicated that <20% of the trichloroethylene was lost from the drinking water solution in a 3- to 4-day period. It is not clear whether the authors included this loss of trichloroethylene with time in their calculations; however, using the dose levels reported, the lowest dose levels, 18.4 mg/kg/day in males and 17.9 mg/kg/day in females, produced no observed effects in the mice. The next dose level of 216.7 mg/kg/day in males and 193.0 mg/kg/day in females caused an increase in the liver-to-body weight ratio in males only. At a dose level of 393.0 mg/kg/day in males and 437.1 mg/kg/day in females, ketone and protein levels were elevated in the urine of males but not females, and the relative liver weight remained higher in males but was not increased in females. At the highest dose levels used in this experiment, 660.2 mg/kg/day for males and 793.3 mg/kg/day for females, both male and female mice had decreased body weights, increased liver and kidney weights, and increased levels of ketone and protein in the urine (Tucker et al., 1982).

In an associated study, groups of male CD-1 mice were given 24 or 240 mg/kg bw trichloroethylene by gavage once a day for 14 days (Sanders et al., 1982). Cell-mediated immune response to sheep erythrocytes was significantly inhibited at both dose levels compared to vehicle controls. Humoral immune response to sheep erythrocytes was unaffected by treatment.

TABLE 3-1

Effects of Subchronic Trichloroethylene Exposure

Route	Dose/Exposure	Duration of Exposure	Species/Strain	Sex	Number Tested	Effect	Reference
Inhalation	control 35 ppm	NA continuous for 90 days	rats/Long-Evans	NR NR	304 15	The only effect was depressed body weight in the three treated rabbits. No effects in any species were seen on survival, hematological values or gross or histological appearance of the internal organs.	Prendergast et al., 1967
	control 35 ppm	NA continuous for 90 days	rabbits/ New Zealand	NR NR	48 3		
	35 ppm	continuous for 90 days	guinea pigs/ Hartley	NR	15		
	35 ppm	continuous for 90 days	squirrel monkeys	NR	3		
	35 ppm	continuous for 99 days	beagle dogs	NR	2		
Inhalation	control 55 ppm (300 mg/m³)	NA 8 hours/day, 5 days/week for 14 weeks	rats/SPF Wistar	M M	20 20	Increased liver weights observed in treated rats. No effects on hepatic or renal function, hematologic values, gross appearance of internal organs or behavior of animals. No histopathological evaluation presented.	Kimmerle and Eben, 1973
Oral, catalpher in water	control vehicle control 18.4 mg/kg/day 216.7 mg/kg/day 393.0 mg/kg/day 660.2 mg/kg/day	NA for 6 months	mice/CD-1	M	140 260 140 140 140 140	Body weights of males and females exposed to the highest dose were significantly lower. In males, liver weight (as a percentage of body weight) was increased at 216.7, 393.0 and 660.2 mg/kg/day; in females, increased liver weight was seen at a dose of 793.3 mg/kg/day. Increased kidney weights occurred in males exposed to 660.2 mg/kg/day and in females exposed to 793.3 mg/kg/day trichloroethylene. Elevated ketone and protein levels in urine were seen at the highest dose in both males and females, and at a dose of 393.0 mg/kg/day in males.	Tucker et al., 1982
	control vehicle control 17.9 mg/kg/day 193.0 mg/kg/day 437.1 mg/kg/day 793.3 mg/kg/day	NA for 6 months	mice/CD-1	F	140 260 140 140 140 140		

12/29/87

TABLE 3-1 (cont.)

Route	Dose/Exposure	Duration of Exposure	Species/Strain	Sex	Number Tested	Effect	Reference
Oral, emulpher in water	control vehicle control 18.4 mg/kg/day 216.7 mg/kg/day 393.0 mg/kg/day 660.2 mg/kg/day	NA for 6 months	mice/CD-1	M	140 260 140 140 140 140	Suppressed humoral immune response to sheep erthrocytes at ≥17.9 mg/kg/day in females after 4 months; suppressed cell mediated immune response to sheep erythrocytes at ≥17.9 mg/kg/day after 4 months and at 793.3 mg/kg/day after 6 months in females. Bone marrow stem cell colonization was significantly inhibited in females at all dose levels after 4 or 6 months and in males at all dose levels after 6 months	Saunders et al., 1982
	control vehicle control 17.9 mg/kg/day 193.8 mg/kg/day 437.1 mg/kg/day 793.3 mg/kg/day	NA for 6 months	mice/CD-1	F	140 260 140 140 140 140		

NA = Not applicable; NR = not reported

Immune status was also evaluated in male and female CD-1 mice that were administered trichloroethylene in the drinking water for 4 or 6 months (Sanders et al., 1982). Reported average doses for 6 months were 0, 18.4, 216.7, 393.0 or 660.2 mg/kg/day for males and 0, 17.9, 193.0, 437.1 or 793.3 mg/kg/day for females. Parameters evaluated included humoral immunity, cell-mediated immunity, lymphocyte responsiveness, bone marrow function and macrophage function. Treatment-related effects included suppressed humoral response to sheep erythrocytes at $\geq$437.1 mg/kg/day after 4 months but not after 6 months in the females (this was supported by concommitant increases in hemagglutination titer), suppressed cell-mediated immune response to sheep erythrocytes at $\geq$17.9 mg/kg/day after 4 months and at 793.3 mg/kg/day after 6 months in the females. Bone marrow stem cell colonization was significantly inhibited in females at all dose levels after 4 and 6 months and in males at all doses after 4 months.

Preliminary subchronic studies for NTP (1986) carcinogenicity bioassays were conducted in which groups of 10 ACI, August or Marshall rats/sex were exposed to trichloroethylene in corn oil by gavage, 5 days/week for 13 weeks. Male ACI and male August rats were administered doses of 0, 125, 250, 500, 1000 or 2000 mg/kg. Female August and female ACI rats were administered doses of 0, 62.5, 125, 250, 500 or 1000 mg/kg. Male Marshall rats were treated with 0, 268, 308, 495, 932 or 1834 mg/kg, and female Marshall rats were treated with 0, 134, 153, 248, 466 or 918 mg/kg. With the exception of three male August rats that were given 2000 mg/kg, all rats survived to termination of the study. Reduced final mean body weights in excess of 10% of control group weights occurred in males of all strains at the high doses; body weight depression ranged from 12.1% in Marshall rats to 17.1% in ACI rats. There were no treatment-related behavioral or histopathological effects in any of the groups.

In preliminary subchronic studies for the NCI (1976) bioassay, 0, 562, 1000, 1780, 3160 or 5620 mg/kg doses of trichloroethylene in corn oil were administered to groups of five Osborne-Mendel rats/sex, 5 days/week for 8 weeks. Groups of five B6C3F1 mice/sex were treated similarly with doses of 0, 1000, 1780, 3160, 5260 or 10,000 mg/kg. Body weight gains of all treated groups of rats were reported to be below that of the control group, and were quantified as >20% for females at doses >1780 mg/kg and males at doses >3160 mg/kg. Abnormal clinical signs at >1780 mg/kg and 100% mortality at 5620 mg/kg also occurred in male and female rats, but there were no treatment-related histopathological effects. There were no treatment-related effects on body weight or histology in the mice, but mortality occurred at 5260 mg/kg (80%) and 10,000 mg/kg (100%).

Results of 13-week preliminary subchronic studies for a NTP (1982) bioassay of trichloroethylene with F344 rats and B6C3F1 mice were not included in the available summary (U.S. EPA, 1985) of this bioassay.

3.1.2. Inhalation. In an earlier study, Adams et al. (1951) reported that exposure to trichloroethylene vapor 7 hours/day, 5 days/week for ~6 months decreased body weights in guinea pigs at a dose level of 200 ppm. At a dose level of 400 ppm, rats had increased liver and kidney weights, and guinea pigs and rabbits had increased liver weights. Male rats and male guinea pigs had depressed body weights at a dose level of 400 ppm (Adams et al., 1951). Rats exposed to 55 ppm trichloroethylene vapor intermittently for 14 weeks (see Table 3-1) had increased liver weights, but no histopathology was reported (Kimmerle and Eben, 1973). Hepatic and renal physiology, as well as clinical hematological values, appeared normal. Prendergast et al. (1967) did not see any effects associated with continuous inhalation of 35 ppm trichloroethylene by rats, guinea pigs, monkeys or

dogs. Depressed body weight was observed in rabbits. Except for the rats, these authors used extremely small numbers of animals and only one dose level. Controls were described only for rats and rabbits.

Rats that were exposed continuously to 320 ppm trichloroethylene for 30 or 90 days had altered fatty acid composition of cerebral cortex ethanolamine phosphoglyceride (Kyrklund et al., 1985 abstract only). Several linoleic acid derived fatty acids were increased and linolenic acid derived fatty acid were decreased. The effects were partially reversed after 30 days rehabilitation and not observed after 5 days of exposure. Continuous exposure to 60 or 300 ppm trichloroethylene for 3 months followed by a recovery period of 4 months had inconclusive effects on brain S100 protein or DNA content in gerbils (Haglid et al., 1981 abstract only).

Groups of 10-20 NMRI mice of both sexes were exposed to 0 or 150 ppm trichloroethylene continuously for 2, 5, 9, 16 or 30 days (Kjellstrand et al., 1981). Groups of 10-24 rats and 8-24 gerbils were similarly exposed to 150 ppm for 30 days. Relative liver weights were increased in all species and treatment groups, but the effect was more pronounced in the mice (60-80% enlargement) than the rats or gerbils (20-30%). Examination of mice 5 and 30 days after cessation of treatment indicated that liver weights had decreased but were still significantly higher than controls. Pathological examinations were not conducted.

In a related study, liver weights and plasma butyrylcholinesterase (BuChE) activity were evaluated in NMRI and nine other strains of mice of both sexes that were exposed to 150 ppm trichloroethylene continuously for 30 days (Kjellstrand et al., 1983b). Unexposed mice of each strain were used for controls. Liver weights were significantly increased in treated mice of all strains and plasma BuChE activity increased in males of all

strains and in females of two of the strains (A/sn and NZB). Pathological examinations were not conducted.

Relative liver weight and BuChE activity were also evaluated in groups of NMRI mice of both sexes that were exposed to 0, 37, 75, 150 or 300 ppm trichloroethylene continuously for 30 days (Kjellstrand et al., 1983a). Group sizes were 20 (10/sex) at 37 ppm and 10 (5/sex) ar the higher concentrations. Liver weights were significantly increased and concentrations-related in all groups (~25% increase at 37 ppm), and BuChE activity was significantly increased in males at 75 and 150 ppm and both sexes at 300 ppm. Intermittent exposure 30-day experiments in which exposures ranged from 225 ppm for 16 hours/day to 3600 ppm for 1 hour/day, providing average daily concentrations of 150 ppm, suggested that liver weight increases were independent of exposure schedule. Histological examination of the livers from an unspecified number of mice showed that continuous exposure to trichloroethylene caused alterations, including enlarged and vacuolated hepatocytes, at all concentrations. The histologic alterations generally were more pronounced following intermittent exposure to the higher concentrations of trichloroethylene. Liver weights and serum BuChE activity were not significantly increased in mice 120 days after continuous exposure to 150 ppm for 30 days. The liver became histologically similar to controls during the rehabilitation period except for changes in cellular and nuclear sizes, suggesting reversibility of the hepatic effects.

The results of a study in which groups of 13 Sprague-Dawley rats were exposed continuously to trichloroethylene concentrations of 0, 50, 200 or 800 ppm for 12 weeks were reported by Nomiyama et al. (1986). Increases in liver weight and hepatic indices apparently occurred in all of the treatment groups (it was reported that effects were noted "especially" in the 800 ppm

group). Hepatic indices measured included total protein, albumin/globulin ratio, SGPT, triglycerides, cholesterol and cholinesterase. Unspecified pathological examinations appear to have been unremarkable.

3.2. CHRONIC

3.2.1. Oral. In the NCI (1976) carcinogenicity bioassay, technical grade trichloroethylene was administered by gavage to groups of 50 Osborne-Mendel rats/sex at TWA doses of 869 or 1739 mg/kg, 50 male B6C3F1 mice at TWA doses of 1169 or 2339 mg/kg and 50 female B6C3F1 mice at TWA doses of 869 or 1739 mg/kg, 5 days/week for 78 weeks, with 12 weeks (mice) or 32 weeks (rats) of observation (Section 4.2.1.). Vehicle controls consisting of 20 animals/sex/species were maintained. Treated rats had decreased body weights and survival times, as well as slight to moderate degenerative and regenerative alterations of renal tubules at both dose levels; however, the control rats also had poor survival and it is difficult to determine the impact of trichloroethylene on survival. The mice did not have decreased body weights or survival times after treatment with trichloroethylene. Treated rats of both sexes had an increased incidence of chronic nephropathy, compared with controls. No noncancerous histopathological changes were described in mice (NCI, 1976).

In the NTP (1982) bioassay, F344 rats of each sex were treated by gavage with 0, 500 or 1000 mg/kg trichloroethylene, 5 days/week for 103 weeks (Section 4.2.1.). B6C3F1 mice of each sex were treated similarly at a dose level of 1000 mg/kg. Treatment-related nonneoplastic effects included reduced weight gain in the low and high dose male and female rats, decreased survival in the low and high dose male rats and toxic nephrosis (characterized as cytomegaly) in 98% of treated male and 100% of treated female rats. Effects in the mice included reduced body weight gain and decreased survival

in the males, and cytomegaly in the kidney of 90% of the treated males and 98% of the treated females. It should be noted that there were neoplastic effects in the kidneys of the rats and liver of the mice (Section 4.2.1.).

Groups of 50 ACI, August, Marshall or Osborne-Mendel rats/sex were administered trichloroethylene by gavage at doses of 0, 500 or 1000 mg/kg, 5 days/week for 103 or 104 weeks (NTP, 1986). The final body weights of all dosed groups, except for high dose female Osborne-Mendel rats, were somewhat lower than those of the control groups, but reductions >10% occurred at 1000 mg/kg in ACI, August and Osborne-Mendel males and Marshall females, and at 500 mg/kg in ACI males. Treatment-related decreased survival occurred in ACI males and Marshall females at both doses and in ACI females and Osborne-Mendel females at 1000 mg/kg. Nonneoplastic pathologic effects included cytomegaly of renal tubular cells and toxic nephropathy in dosed rats of all strains; incidences ranged from 82-98% and 17-80% for the two types of lesions, respectively. Treatment-related neoplastic renal lesions also occurred (Section 4.2.1.).

3.2.2. Inhalation. A number of epidemiologic studies with occupational exposure to trichloroethylene, primarily oriented toward carcinogenicity, have been reviewed by U.S. EPA (1985) and Axelson (1986). The more extensive review and evaluation was performed by U.S. EPA (1985). Of the epidemiologic studies, two (Axelson et al., 1978; Tola et al., 1980) reported the total number of observed deaths from all causes compared with the number of expected deaths based on national statistics (for Sweden and Finland, respectively). In neither study did the number of observed deaths significantly exceed the number expected, and in most cases the number observed was substantially below the number expected.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Pertinent data regarding teratogenicity resulting from oral exposure to trichloroethylene could not be located in the available literature.

Reproductive function was assessed in groups of ten 70-day-old male Long-Evans rats that were treated with trichloroethylene in corn oil by gavage at doses of 0, 10, 100 or 1000 mg/kg, 5 days/week for 6 weeks (Zenick et al., 1984). Copulatory behavior and semen evaluations (sperm count, motility and morphology) were conducted after 1 and 5 weeks of treatment and at 4 weeks postexposure. Impaired copulatory behavior, characterized by neglect of females and incomplete genital contact, occurred in the 1000 mg/kg group only after 1 week of exposure. It was suggested that these effects may be attributed to the narcotic properties of trichloroethylene, as they were not apparent after 5 weeks of treatment because of presumed tolerance.

Groups of 22 or 23 female Long-Evans rats were exposed to trichloroethylene in corn oil by gavage at doses of 0, 10, 100 or 1000 mg/kg for 2 weeks before mating through day 21 of pregnancy (Manson et al., 1984). There were no effects on length of estrus cycle or fertility in any of the groups. Maternal toxicity (increased mortality and decreased weight gain) and decreased neonatal survival, which were primarily due to deaths at the time of birth, occurred at 1000 mg/kg.

Trichloroethylene that was microencapsulated in a gelatin/sorbitol shell was administered in the diet to CD-1 mice in a continuous breeding fertility study that consisted of a 7-day premating exposure period, a 98-day cohabitation period and a 21-day segregation period (George et al., 1986a). Diet concentrations of 0, 0.15, 0.30 and 0.60% provided respective approximate trichloroethylene intakes of 0, 64, 248 and 653 mg/kg/day during the first

week, 0, 53, 266 and 615 mg/kg/day during the second week and 0, 188, 375 and 750 mg/kg/day during the remainder of the study. Thirty-five pairs of untreated and 17-19 pairs of treated mice were tested. Final litters from the control and high dose-groups were raised to sexual maturity and bred. There were no treatment-related effects on fertility or reproductive performance in either the F_0 or F_1 mice but sperm motility was reduced by 45% in the high dose F_0 males and by 18% in the F_1 males. Effects in high-dose F_1 offspring included increased testis and epididymidis weights and a 2-fold decrease in perinatal (days 0-21) but not postweaning survival. Histological examination of tissues revealed treatment-related lesions in the liver and kidneys (but not in the reproductive tracts) in the high-dose F_0 and F_1 mice.

A similarly designed fertility study with microencapsulated trichloroethylene was conducted with F344 rats (George et al., 1986b). This study used the same diet concentrations as the mouse study (intake estimates were not reported) and similar numbers of animal pairs, but differed with respect to the segregation period (28 days as opposed to the previously used 21 days). Treatment at all concentrations had a marginal effect on numbers of live litters per pair and live pups per litter, but no effect on fertility or other measures of reproductive performance. Rats in the high concentration group had increased testis and epididymis weights, but sperm evaluations, testis histology and histology of other tissues were normal. There were no effects on fertility, reproductive performance, histology or open field behavioral performance in the F_1 generation. The effects indicated in the George et al. (1986b) study were attributed to generalized toxicity rather than a specific effect on the reproductive system because decreased body and organ weights occurred in both F_0 and F_1 rats.

3.3.2. Inhalation. When Swiss-Webster mice and Sprague-Dawley rats were exposed to trichloroethylene vapor at a concentration of 300 ppm for 7 hours/day on days 6-15 of gestation (Schwetz et al., 1975), no treatment-related increase in malformations was seen; however, slightly reduced fetal body weight, delayed skeletal development and an increase in the incidence of undescended testes were observed in mice. Decreased maternal weight gain occurred in the rats.

Healy et al. (1982) exposed 32 mated Wistar rats to trichloroethylene at 100 ppm 4 hours/day on days 8-21 of gestation. A group of 31 similarly treated mated rats served as controls. Examinations performed on gestation day 21 revealed no evidence of teratogenicity, but fetotoxicity was manifested as an increase in the incidence of dams with complete litter resorptions, reduced fetal body weight and delayed ossification. No mention was made of maternal toxicity.

When pregnant rabbits were exposed to trichloroethylene vapor at a concentration of 500 ppm 7 hours/day, 5 days/week on days 6-21 of gestation, days 0-21 of gestation or beginning 3 weeks before mating continuing through gestation, the offspring were reported to have an increased incidence of external hydrocephalus (Beliles et al., 1980). While the incidence was not statistically significant, the authors felt that it was biologically significant. Other, less definitive, teratogenicity studies include those of Taylor (1936), Bell (1977), Dorfmueller et al. (1981) and York et al. (1981). Generally, the only effects observed were reduced fetal body weight and body size and delayed ossification.

3.4. TOXICANT INTERACTIONS

Because trichloroethylene is bioactivated by liver microsomal enzymes, substances that stimulate liver microsomal enzymes may potentiate trichloroethylene toxicity, and substances that depress liver microsomal enzymes may

decrease trichloroethylene toxicity (U.S. EPA, 1985). In addition, interactions with alcohol (Bardodej and Vyskoch, 1956; Seage and Burns, 1971; Cornish and Adefuin, 1966; Ferguson and Vernon, 1970; Gessner and Cabana, 1970) and carbon tetrachloride (Pessayre et al., 1982) enhance the toxicity of trichloroethylene. Trichloroethylene potentiates the effect of epinephrine on the myocardium (Dhumer et al., 1957; Defalque, 1961).

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Although trichloroethylene has been reported as a contaminant of various human water supplies (Ziglio et al., 1983), pertinent data regarding carcinogenicity in humans from oral exposure to trichloroethylene were not located in the available literature.

4.1.2. Inhalation. Three retrospective epidemiologic studies investigating human exposure to trichloroethylene in the workplace and subsequent tumor development (Axelson et al., 1978; Blair et al., 1979; Tola et al., 1980) were reviewed in U.S. EPA (1985). Individuals in these studies were assigned to exposure categories on the basis of the amount of trichloroacetic acid, a trichloroethylene metabolite, in their urine or plasma. In the only study to find a significant increase in the incidence of cancer in exposed individuals (Blair et al., 1979), the workers had been exposed to tetrachloroethylene and carbon tetrachloride in conjunction with trichloroethylene. The relative amounts of each chemical during exposure were not determined. The other two studies (Axelson et al., 1978) did not find an increased incidence or rate of cancer development in individuals exposed to trichloroethylene.

A more recent study (Shindell and Ulrich, 1985), which is reviewed in detail in U.S. EPA (1987b), reports the results of a cohort study in a manufacturing plant where trichloroethylene was used as a degreasing agent. This study failed to demonstrate any cause-specific excess mortality. However, data concerning exposure level, duration of exposure and follow-up were inadequate. The conclusions of U.S. EPA (1987b) were that these data were inadequate to fully evaluate the absence of an effect.

4.2. BIOASSAYS

4.2.1. Oral. In the NCI (1976) study, groups of ~50 B6C3F1 mice/sex and similar numbers of Osborne-Mendel rats were given trichloroethylene in corn oil by gavage, 5 days/week for 78 weeks (Table 4-1). The mice were 5 weeks old at their first treatment and the rats were 7 weeks old. The trichloroethylene was ≥99% pure but contained epoxide stabilizers, including 0.09% epichlorohydrin. The experiments were terminated after 90 weeks (mouse) and 110 weeks (rat). The doses specified in Table 4-1 are TWA doses calculated for the 5 days/week of treatment (the doses were changed during the course of the experiments). No compound-related carcinogenic effects were seen in the rats, but high mortality rates within all groups of rats significantly detracted from the usefulness of the conclusions (U.S. EPA, 1985). There was a significant increase in the incidence of hepatocellular carcinomas in male mice at both dose levels. Females had a significantly increased incidence of hepatocellular carcinomas, but only at the high dose level. The carcinogenic effect of trichloroethylene was greater in males than females. The rate of hepatocellular tumor development was dose-dependent, being greater in the male animals exposed to the high dose level (NCI, 1976).

The National Toxicology Program (NTP, 1982) recently completed a cancer bioassay using Fisher 344 rats. The trichloroethylene used had a purity >99.9% and epichlorohydrin was not detected in samples (detection level 0.001% v/v). Fifty male and 50 female rats were assigned to the following treatment groups: untreated control, vehicle control, 500 mg/kg trichloroethylene, 1000 mg/kg trichloroethylene. Trichloroethylene was administered in corn oil by gavage, 5 days/week for 103 weeks.

A dose-related reduction in survival was noted in male rats (NTP, 1982). Both the low and high dose groups were significantly different from the vehicle control group using survival probabilities estimated by the Kaplan

TABLE 4-1

Carcinogenicity of Trichloroethylene

Route	Dose/Exposure	Duration of Treatment	Length of Experiment	Species/ Strain	Sex	Number Treated	Target Organ	Comments	Reference
Oral[a]	0 1119 mg/kg/day 2339 mg/kg/day	5 days/week for 78 weeks	90 weeks	mouse/ B6C3F1	M M M	20 50 48	liver	Hepatocellular tumors occurred in 26/50 (low-dose) and 31/48 (high-dose) of the treated males as compared with 1/20 control male mice ($p<0.05$ for both dose levels)	NCI, 1976
	0 869 mg/kg/day 1739 mg/kg/day	5 days/week for 78 weeks	90 weeks		F F F	20 50 47	liver	Hepatocellular tumors occurred in 4/50 (low-dose) and 11/47 (high-dose) of the treated females as compared with 0/20 control female mice ($p<0.05$ for the high-dose level only)	
	0 549 mg/kg/day 1097 mg/kg/day	5 days/week for 80 weeks	110 weeks	rat/ Osborne-Mendel	F/M F/M F/M	100/100 50/50 50/50	none	No carcinogenic effects were seen in rats.	
Oral[a]	untreated control vehicle control 500 mg/kg 1000 mg/kg	5 days/week, 103 weeks	103 weeks	rat/ Fisher 344	F/M	50/50 50/50 50/50 50/50	kidney	High-dose males showed significant increase in kidney adenocarcinomas. Assay deemed inadequate by NTP.	NTP, 1982
Oral[a]	untreated control vehicle control 1000 mg/kg	5 days/week, 103 weeks	103 weeks	mouse/ B6C3F1	F/M	50/50 50/50 50/50	liver	Significant incidence of hepatocellular carcinoma in treated males and females.	NTP, 1982
Oral[b]	0 500 mg/kg 1000 mg/kg	5 days/week, 103-104 weeks	103-104 weeks	rat/ACI, August, Marshall, Osborne-Mendel	F/M	50/sex/ strain/ dose	none	Increased incidences of renal tubular cell adenomas in the low dose Osborne-Mendel males (6/50 vs. 0/50 in controls) and testis interstitial cell tumors in the high-dose Marshall males (32/48 vs. 17/46). Assays deemed inadequate by NTP.	NTP, 1986
Oral[b]	vehicle control 50 mg/kg 250 mg/kg	4-5 days/week for 52 weeks	140 weeks	rat/ Sprague-Dawley	F/M F/M F/M	30/30 30/30 30/30	none	Slight increase in mortality in females. Dose-dependent increase in renal mononucleocytosis in males. Slight increase in leukemia in males (3.3%, 6.7% and 10% for the 0, 50 and 250 mg/kg groups) and lymphosarcoma in males (0, 6.7 and 3.3%).	Maltoni, 1986

TABLE 4-1 (cont.)

Route	Dose/Exposure	Duration of Treatment	Length of Experiment	Species/ Strain	Sex	Number Treated	Target Organ	Comments	Reference
Inhalation	0 100 ppm 300 ppm 600 ppm	6 hours/day, 5 days/week for 24 months	24 months	mouse/ B6C3F1	M M M M	99 95 100 97	liver	Hepatocellular carcinoma was reported in 28/95, 31/100 and 43/97 male mice exposed to 100, 300 and 600 ppm, respectively, of trichloroethylene. Controls had 18/99 mice with hepatocellular tumors ($p<0.05$ for comparison between treated and control mice)	Bell et al., 1978
	0 100 ppm 300 ppm 600 ppm	6 hours/day, 5 days/week for 24 months	24 months	mouse/ B6C3F1	F F F F	99 100 94 99	liver	Hepatocellular carcinoma was reported in 4/100, 9/94 and 13/99 female mice exposed to 100, 300 and 600 ppm, respectively, of trichloroethylene. Controls had 0/99 mice with hepatocellular tumors ($p<0.05$ for comparison between 600 ppm group and controls)	
	0 100 ppm 300 ppm 600 ppm	6 hours/day, 5 days/week for 24 months	24 months	rat/ Charles River	F/M F/M F/M	NA	none	No carcinogenic response.	
Inhalation	0 50 ppm 150 ppm 450 ppm	7 hours/day, 5 days/week for 104 weeks	107 weeks	mouse/ IRC	F F F F	49-50 49-50 49-50 49-50	lung	Mice exposed to 150 and 450 ppm trichloroethylene had 3 times the number of lung tumors observed in the low-dose animals and the controls. A statistically significant increase was seen when the number of lung adenocarcinomas in mice exposed to 150 and 450 ppm trichloroethylene was compared with the number of lung adenocarcinomas in the low-dose and control animals. Incidences were 1/49, 3/50, 8/50 and 7/46 for the 0, 50, 150 and 450 ppm groups.	Fukuda et al., 1983
	0 ppm 50 ppm 150 ppm 450 ppm	7 hours/day, 5 days/week for 104 weeks	107 weeks	rat/SD	F F F F	49-51 49-51 49-51 49-51	none		
Inhalation	0 ppm 100 ppm 300 ppm 600 ppm	7 hours/day 5 days/week for 108 weeks	159 weeks	rat/ Sprague-Dawley	M/135, F/145 M/F 130 M/F 130 M/F 130		testis	Leydig cell tumors: 4% at 0 ppm 12% at 100 ppm 23% at 300 ppm 24% at 600 ppm	Maltoni et al., 1986

TABLE 4-1 (cont.)

Route	Dose/Exposure	Duration of Treatment	Length of Experiment	Species/ Strain	Sex	Number Treated	Target Organ	Comments	Reference
Inhalation							kidney	Adenocarcinoma (600 ppm only): M 3%, F 1%, other exposure levels 0%	Maltoni et al., 1986
							bone marrow	Leukemia F: 3% at 0 ppm, 7% at 100 ppm, 2% at 300 ppm, 9% at 600 ppm; M: 13% at 0 ppm, 10% at 100 ppm, 11% at 300 ppm, 12% at 600 ppm	
	0 ppm 100 ppm 300 ppm 600 ppm	7 hours/day, 5 days/week for 78 weeks	154 weeks	mouse/ BT305/Swiss	M/F M/F M/F M/F	90 90 90 90	lung, liver	Males showed pulmonary tumors: 11% at 0 ppm, 12% at 100 ppm, 26% at 300 ppm, 30% at 600 ppm and hepatomas: 4% at 0 ppm, 2% at 100 ppm, 9% at 300 ppm and 14% at 600 ppm	
Inhalation	0 ppm 100 ppm 300 ppm 600 ppm	7 hours/day, 5 days/week for 78 weeks	154 weeks	mouse/ B6C3F1 (NCI)	M/F M/F M/F M/F	90 90 90 90	lung, liver	Females, pulmonary tumors: 4% at 0 ppm, 7% at 100 ppm, 6% at 300 ppm and 17% at 600 ppm; hepatomas, females: 3% at 0 ppm, 4% at 100 ppm, 4% at 300 ppm, 10% at 600 ppm males: 2% at 0 ppm, 2% at 100 ppm, 7% at 600 ppm	Maltoni et al. 1986
Inhalation	0 ppm 100 ppm 500 ppm	6 hours/day, 5 days/week for 18 months	30 months	mouse/ Han:NMRI	F F F	29 30 28	lymphatic tissue	Histopathological examinations were made on all animals. No carcinogenic effect was observed in either sex of rats or hamsters, or in male mice. In female mice, the incidence of lymphomas was higher in the low-dose (17/30) and the high-dose (18/28) groups of animals than in the control (9/29) group.	Henschler et al., 1980
	0 ppm 100 ppm 500 ppm				M M M	30 30 30	none		
	0 ppm 100 ppm 500 ppm	6 hours/day, 5 days/week for 18 months	36 months	rat/ Wistar	F/M F/M F/M	30/30 30/30 30/30	none		
	0 ppm 100 ppm 500 ppm	6 hours/day, 5 days/week for 18 months	30 months	hamster/ Syrian	F/M F/M F/M	30/30 30/30 30/30	none		

[a]Vehicle was corn oil

[b]Vehicle was olive oil

N/ - Not available

and Meier technique. High dose males showed a significant ($p<0.05$) increase in kidney tubular adenocarcinomas (3/16) compared with vehicle controls (0/33) at terminal sacrifice by life table ($p=0.028$) and incidental tumor ($p=0.028$) tests. The Cochran-Armitage test for linear trend was also significant ($p=0.038$). Historical control data showed a renal tumor incidence of 3/748 for this strain of rat; however, the comparison of kidney adenocarcinomas between high dose males and vehicle controls did not show a significant difference using the Fisher Exact test. Other treatment-related increases in tumor incidence were not apparent. The high dose used in this study appears to have exceeded the maximally tolerated dose as defined by NCI. Despite the increase in renal adenocarcinomas, NTP has concluded that this study is inadequate for judging the carcinogenicity of trichloroethylene.

B6C3F1 mice were also tested in this study (NTP, 1982). A single gavage dose of 1000 mg/kg/day trichloroethylene in corn oil, 5 days/week for 103 weeks was used. Fifty males and 50 females were assigned to the untreated control, vehicle control and trichloroethylene groups. Body weights and survival were reduced in treated males when compared with vehicle controls. There was a significant ($p<0.002$) increase in incidence of hepatocellular carcinoma in treated male and female mice. Females showed incidences of 2/48 and 13/49 in the vehicle and treated groups, respectively. The corresponding incidences in males were 8/48 and 30/50. In addition, hepatocellular adenoma incidence was significantly ($p<0.05$) increased in female mice by the life table, incidental tumor and Cochran-Armitage and Fisher Exact tests, while in males significance was only found using life table analysis. Historical control data indicated hepatocellular tumor incidence of 18% and 2.9% for males and females, respectively. These results confirm those of the NCI (1976) study that reported an increased incidence of hepatocellular

carcinoma in male and female B6C3F1 mice given trichloroethylene stabilized with epichlorohydrin and other epoxides. These results indicate that the epoxides were not a requisite factor in the response.

Groups of 50 ACI, August, Marshall or Osborne-Mendel rats/sex were administered epichlorohydrin-free trichloroethylene in olive oil by gavage at doses of 0, 500 or 1000 mg/kg, 5 days/week for 103 or 104 weeks (NTP, 1986). Treatment was associated with significantly increased incidences of renal tubular cell adenomas in the low dose male Osborne-Mendel rats and interstitial cell tumors of the testis in high dose male Marshall rats. NTP (1986) concluded that these bioassays were inadequate for assessing either the presence or absence of carcinogenicity because of chemically induced toxicity and reduced survival (see Section 3.2.1.), and deficiencies in the conduct of the studies as revealed by data audits.

Maltoni et al. (1986) treated male and female Sprague-Dawley rats by gavage with trichloroethylene (99.9% pure) in olive oil at 50 or 250 mg/kg, 4-5 days/week for 52 weeks. The rats were observed until death. There was a dose related increase in the incidence of leukemia and immunoblastic lymphosarcomas in males, with no increased tumor incidence in females. The rats were 13 weeks old before trichloroethylene treatment began. As a part of a much larger experiment, Van Duuren et al. (1979) treated 30 male and 30 female ICR/Ha Swiss mice by gavage with 0.5 µg trichloroethylene once a week for 622 days. No effects were reported.

4.2.2. Inhalation. Bell et al. (1978) reported the Manufacturing Chemists Association's audit findings on a bioassay conducted from 1975-1977 at Industrial Bio-Test Laboratories, Inc. In this study, mice and rats were exposed to 100, 300 or 600 ppm of trichloroethylene 6 hours/day, 5 days/week for 24 months (see Table 4-1). No carcinogenic effect was seen in rats. Hepatocellular carcinoma occurred in mice. In males, the incidence of

hepatocellular carcinoma was greater at each dose level than in females and occurred at all dose levels tested. Hepatocellular carcinoma occurred at a significantly increased incidence in females only at the highest dose level. Several problems, including greatly vacillating exposure levels and replacement of animals during the experiment, challenge the validity of the results (U.S. EPA, 1982).

Female ICR mice and SD rats were exposed to 50, 150 and 450 ppm of trichloroethylene 7 hours/day, 5 days/week (Fukada et al., 1983) (see Table 4-1). Exposure began for both mice and rats at 7 weeks of age. No significant effects on body weight or mortality were produced by trichloroethylene. After 1 year of exposure, some animals developed bloody nasal discharge (rats), local alopecia (mice and rats), respiratory disorders (mice and rats) or a hunching appearance (mice), but the incidence and duration of these clinical observations were not discussed by the authors. Although hematopoietic and mammary tumors in mice and pituitary and mammary tumors in rats occurred frequently, the only tumor type that occurred significantly more frequently in treated compared with control animals was lung adenocarcinoma in mice. The development appeared dose-related and species-specific in that 150 and 450 ppm trichloroethylene caused an increased incidence of pulmonary adenocarcinomas in mice only (Fukada et al., 1983).

After exposure to 100 or 500 ppm of trichloroethylene, 6 hours/day, 5 days/week for 18 months, no effect on the body weights of rats, mice or hamsters was observed, and increased mortality was observed only in the mice (Henschler et al., 1980) (see Table 4-1). Age of the animals at the start of exposure was not reported. The only statistically significant effect ($p<0.05$) was an increased incidence and rate of development of malignant lymphomas in female mice. The response was greater, but apparently not significantly greater, in the high dose than in the low dose animals. The

authors suggested that immunosuppression in the female mice was a contributing factor in the increased rate and incidence of the malignant lymphomas, but they provided no experimental basis for the suggestion. The control mice in the Henschler et al. (1980) study had a higher incidence of lymphomas (30%) than the average (16%) reported by Luz (1977). In a preliminary report on a short-term study, Sanders et al. (1980) indicated that 14 days of treatment with 24 or 240 mg/kg of trichloroethylene by gavage decreased the immune response in male CD-1 mice.

Maltoni et al. (1986) conducted a number of inhalation studies in which rats or mice were exposed to trichloroethylene at 0, 100, 300 or 600 ppm, 7 hours/day, 5 days/week. Exposure of Sprague-Dawley rats by this regimen for 8 weeks (observed for 164 weeks) did not result in increased tumor incidences. A slight but nonsignificant increase in hepatomas was observed in male but not female Swiss mice exposed to trichloroethylene for 8 weeks, with a total observation period of 134 weeks.

Exposure of groups of 130 Sprague-Dawley rats of each sex to trichloroethylene by this regimen for 104 weeks (observed for 150 weeks) resulted in a significant dose-related increase in testicular Leydig cell tumors (Maltoni et al., 1986). Slight increases in leukemia, especially immunoblastic lymphosarcomas, and renal adenocarcinomas were also noted among the exposed males. Tumor incidences were not increased among female rats.

Maltoni et al. (1986) also exposed groups of 90 male and 90 female Swiss mice, similar groups of B6C3F1 (NCI) mice, and groups of 90 male B6C3F1 (CRL) mice to trichloroethylene by this regimen for 78 weeks (observed for 154 weeks). Increased incidences of hepatomas (4, 2, 9 and 14%) and lung tumors (11, 12, 26 and 30%) occurred in some of the treated groups of male Swiss mice. The incidences were significantly increased at the high and

mid-exposure concentrations for lung tumors, and at the high concentration for liver tumors. Although lung tumors were not significantly increased in female Swiss mice, the incidence data (15/90, 15/89, 13/90, 20/89) suggested a trend. Incidences of hepatomas (2/90, 4/90, 4/89, 9/89) and pulmonary tumors (2/90, 6/90, 7/89, 14/87) were increased among treated female B6C3F1 (NCI) mice, but the only increase that was statistically significant was pulmonary tumors in the high dose group. The increase in total number of malignant tumors among the females was statistically significant at all exposure levels. The study in male B6C3F1 (CRL) mice was conducted because survival of the male B6C3F1 (NCI) mice was reduced due fighting. Among male B6C3F1 (CRL) mice, tumor incidences were not increased at any of the exposure levels when compared with controls.

4.2.3. Selected Pharmacokinetics Relevant to Dose-Response Estimates. A complete discussion of the pharmacokinetics of trichloroethylene is outside the scope of this document. The pharmacokinetic data are extensively reviewed in U.S. EPA (1985). A brief summary of the data relating to saturation kinetics is included here since these data are an integral part of dose estimates used for quantitative risk assessment for trichloroethylene.

Experimental data indicate that the magnitude of trichloroethylene metabolism is dose-dependent in rodents, showing saturation kinetics in both the mouse and rat at high dose levels. The dose required for saturation appears to be ~2000 mg/kg in mice and between 500 and 1000 mg/kg in rats.

Experimental evidence indicates that metabolic pathways for trichloroethylene are qualitatively similar among mice, rats and humans (U.S. EPA, 1985).

Studies regarding trichloroethylene metabolism considered by U.S. EPA (1985) to be most relevant to interspecies dose-response extrapolation are summarized in the following paragraphs.

Prout et al. (1985) administered ^{14}C-trichloroethylene in corn oil as single intragastric doses of 10, 500, 1000 and 2000 mg/kg to male Osborne-Mendel and Wistar-derived rats and to male B6C3F1 and Swiss mice. Exhaled breath, urine, feces and carcass were analyzed for radioactivity and unmetabolized trichloroethylene for up to 72 hours after dosing. The results of these studies are shown in Table 4-2.

The conclusions drawn from this study by U.S. EPA (1985) were as follows:

1. Virtually complete gastrointestinal absorption of trichloroethylene occurred for all doses in mice and rats.

2. No intraspecies strain differences were apparent.

3. Saturation of metabolism in the mouse began to occur at a dose of 1000 mg/kg based on excretion of unmetabolized trichloroethylene in the expired air.

4. Saturation of metabolism in rats began to occur at 500 mg/kg as indicated by exhalation of unchanged trichloroethylene at this dose level.

Green and Prout (1984) orally dosed rats and mice for 180 days with 1000 mg/kg/day trichloroethylene in corn oil. Metabolism was evaluated by quantifying urinary metabolites (TCA and TCE-glucuronide). These data are shown in Table 4-3. The fractional metabolism appeared to be constant across time although the ratio of TCA to TCE-glucuronide increased. These data indicated that trichloroethylene did not accumulate significantly with repeated daily dosing.

DeKant et al. (1984), using balance studies, compared the metabolism of trichloroethylene in female Wistar rats and female NMRI mice. A single gavage dose of 200 mg/kg ^{14}C-trichloroethylene was administered to each animal. Radioactivity was measured in urine, feces, carcass and exhaled air for 72 hours after administration. Virtually complete oral absorption was apparent. Data are shown in Table 4-4. The amount of trichloroethylene

TABLE 4-2

Disposition of ^{14}C-Trichloroethylene 72 Hours After Single Oral Doses to Male Osborne-Mendel and Wistar-Derived Rats and to Male B6C3F1 and Swiss Mice[a]

Dose (mg/kg)	Mice (mean of 4)			Dose (mg/kg)	Rats (mean of 4)		
	Dose/ Animal[b] (mg)	Metabolized (mg equivalent)	Exhaled (mg equivalent)		Dose/ Animal[b] (mg)	Metabolized (mg equivalent	Exhaled (mg equivalent)
10	0.30	0.28	0.01	10	2.0	1.93	0.03
500	15.0	13.73	0.90	500	100.0	55.40	42.70
1000	30.0	23.28	5.25	1000	200.0	79.00	112.40
2000	60.0	46.90	8.16	2000	400.0	80.40	311.20

[a]Source: U.S. EPA, 1985

[b]Based on experimental weight of animals: rats, average 200 g; mice, 30 g.

TABLE 4-3

Metabolism of Trichloroethylene in B6C3F1 Mice:
Effect of Chronic Dosing[a] (1000 mg/kg/day)[b]

Day	Metabolized (mg equivalent)	Expired Unchanged (mg equivalent)
	CHRONIC	
1	18.27	5.28
10	22.50	4.08
180	15.75	7.11
	SINGLE-DOSE CONTROLS	
1	18.27	5.28
10	19.35	4.62
180	16.86	3.75

[a]Source: U.S. EPA, 1985

[b]Based on experimental weight of mice averaging 30 g, the daily dose per mouse equals 30 mg in 0.5 corn oil.

TABLE 4-4

Disposition of ^{14}C-Trichloroethylene Radioactivity for 72 Hours After Single Oral Doses (200 mg/kg) to Rats and Mice (NMRI)[a]

	Mice (average of 3)[b] Absolute dose 5.1 mg/animal mg equivalent per animal	Rats (average of 2)[b] Absolute dose 48 mg/animal mg equivalent per animal
Expired		
Unchanged	0.56 (11.0%)	24.96 (52.0%)
Metabolized		
$^{14}CO_2$	0.31	0.91
Urine	3.89	19.78
Feces	0.25	0.86
Carcass	0.10	1.39
Washes	0.01	0.10
	4.56 (89.4%)	23.04 (48.0%)
Total	5.12	48.0

[a]Source: U.S. EPA, 1985

[b]Based on experimental weight of animals: female rats, 140 g; female mice, 25.5 g.

metabolized by rats and mice, as estimated by U.S. EPA (1985), is also shown in Table 4-4. Based on these data, U.S. EPA (1985) estimated the ratio of metabolized trichloroethylene as 5.05 for rat:mouse. This ratio agrees well with the estimated surface area ratio for the two species $[(240/24.4)^{0.67} = 4.46]$.

Buben and O'Flaherty (1985) examined trichloroethylene metabolism in male Swiss-Cox mice administered trichloroethylene by gavage 5 days/week for 6 weeks. Doses used were 0, 100, 200, 400, 800, 1600, 2400 and 3200 mg/kg/day. Metabolism was evaluated by monitoring urinary metabolites. These data showed a linear relationship between urinary metabolites for doses in the range of 0-1600 mg/kg trichloroethylene. At higher doses, saturation of metabolism is indicated by an abrupt plateau.

The data of Prout et al. (1985) which were presented in Table 4-2 are illustrated graphically in Figure 4-1. Using least square regression, these data were fitted to a Michaels-Meten type equation of: amount metabolized (M)=594.1 mg x administered dose (d in units of mg/day) ÷ [702.97 mg + d]. This equation was utilized to estimate the animal metabolized doses for each administered dose in the NTP (1982) and NCI (1976) cancer bioassays in mice. Using the conclusions previously discussed, the animal metabolized doses were then converted to human metabolized doses using a surface area ratio.

U.S. EPA (1987b) utilized a similar approach for the development of an inhalation unit risk for trichloroethylene. In this document the data of Prout et al. (1985) (see Table 4-2) were combined with that of Stott et al. (1982) shown in Table 4-5. The pooled data from the inhalation and oral exposures were evaluated using linear regression and the resultant relationships between trichloroethylene exposure (TCI) in units of mg/kg and total trichloroethylene metabolites (TTCIM) in mgs are shown for rats and mice in Figures 4-2 and 4-3, respectively.

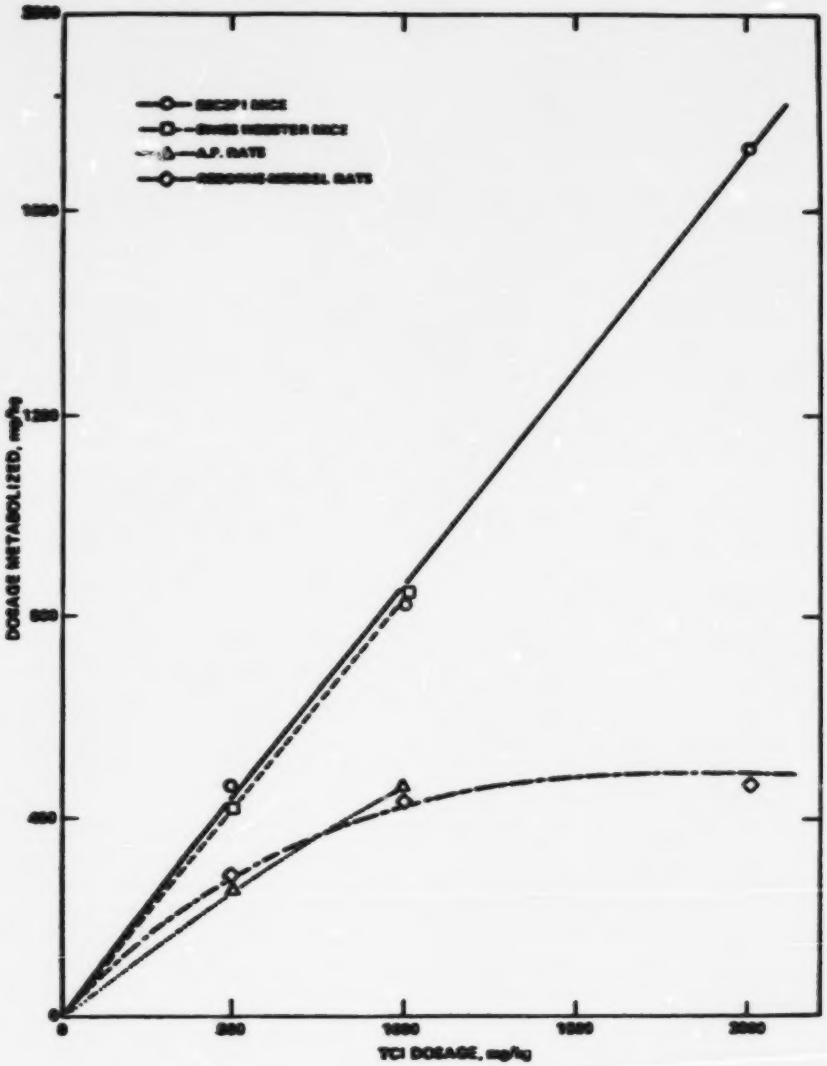

FIGURE 4-1

Relationship between administered single oral doses of ^{14}C-TCl to rats and mice and amount of dose metabolized in 24 hours, expressed as mg/kg bw, as calculated from ^{14}C-radioactivity excreted in urine, feces and expired air (other than unchanged ^{14}C-TCl). Each data point represents four rats or mice.

Source: U.S. EPA, 1985

TABLE 4-5

Metabolism of Radiolabeled Trichloroethylene in Rats and Mice Following a 6-Hour Exposure Period*

ppm	Total uptake (mg/rat)	Exhaled (mg)	Metabolized (mg)
Rats			
10	1.18	0.03	1.15
600	35.31	7.46	27.82
Mice			
10	0.36	0.003	0.36
600	14.4	0.346	14.0

*Source: U.S. EPA, 1987b

Data of Stott et al., 1982

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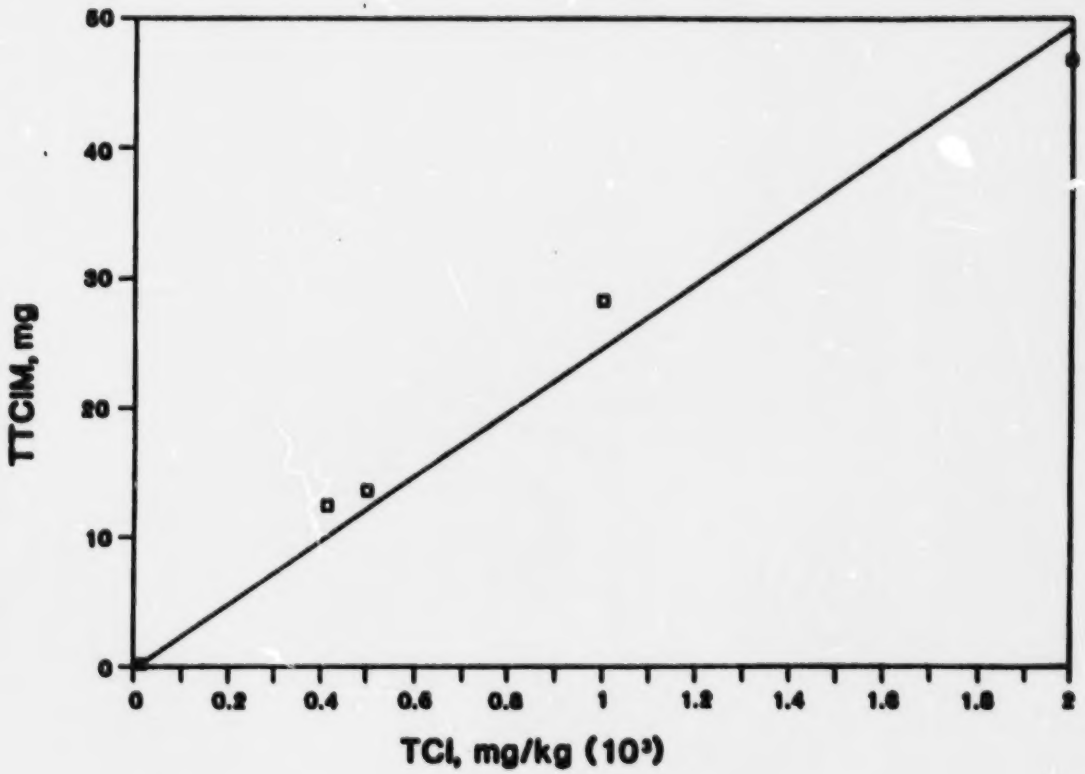

FIGURE 4-2

Relationship in the mouse of the doses of TCI (po mg/kg: inhalation mg eq/kg) and the amount of total TCI metabolized (TTCIM mg eq). The input data are based on information given in Tables 4-2 and 4-4. The linear regression was $0 + 0.0247\ x = y$ $r^2 = 0.98$.

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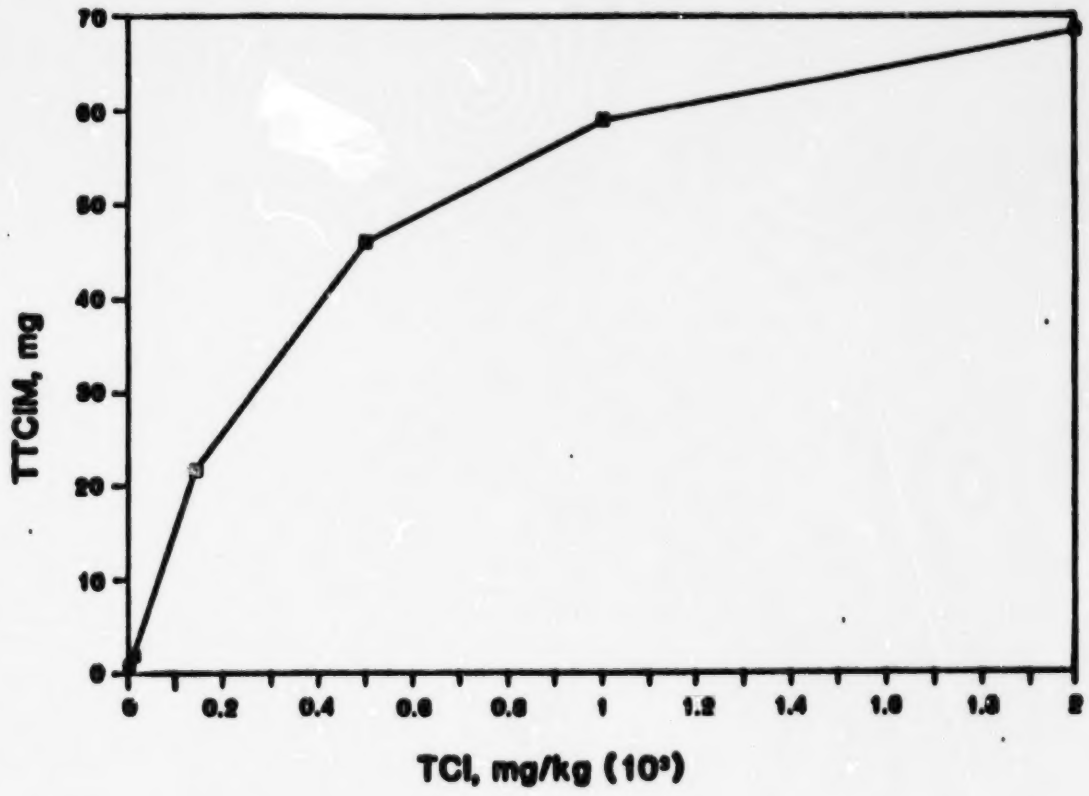

FIGURE 4-3

Relationship in the Rat of the Doses of TCI (po mg/kg: inhalation mg eq/kg) and the Amount of Total TCI Metabolized (TTCIM mg eq) as Predicted by Using Data From Tables 4-2 and 4-5

Source: U.S. EPA, 1987b

Transformation of these curves into ppm exposure vs. metabolized dose are shown in Figures 4-4 and 4-5 for rats and mice, respectively. These curves were constructed by first estimating the amount of trichloroethylene inhaled using estimated ventilating volumes. These curves illustrate a two-compartment solution with a log-log solution in the first compartment and a Lineweaver-Burk solution for the second compartment.

The data from Figures 4-4 and 4-5 are presented in tabular form in Table 4-6. It is these metabolized dose estimates which form the basis for the quantitative risk estimates for inhalation exposure.

4.3. OTHER RELEVANT DATA

Trichloroethylene is often contaminated with carbon tetrachloride, chloroform, epoxides and other chemicals (Henschler et al., 1977; Loprieno et al., 1979), some of which are mutagenic. In order to eliminate the mutagenicity caused by contaminants, purified trichloroethylene has been tested. Purified trichloroethylene caused increased mutagenesis in Salmonella typhimurium (Bartsch et al., 1979; Baden et al., 1979; Simmon et al., 1977), and in Saccharomyces cerevisiae, strains D4 and D7 (Bronzetti et al., 1978) only after metabolic activation (U.S. EPA, 1981). Abrahamson and Valencia (1980) reported negative results in testing for sex-linked recessive lethal mutations in Drosophila melanogaster. Trichloroethylene did not induce dominant lethal mutations in NMRI-Han/BGA mice (Slacik-Erben et al., 1980). Results of mutagenicity testing in the mouse spot test, however, were positive (Fahrig, 1977).

Negative results were observed in mouse skin painting and subcutaneous injection studies with trichloroethylene (Van Duuren et al., 1979) and trichloroethylene epoxide (Van Duuren et al., 1983).

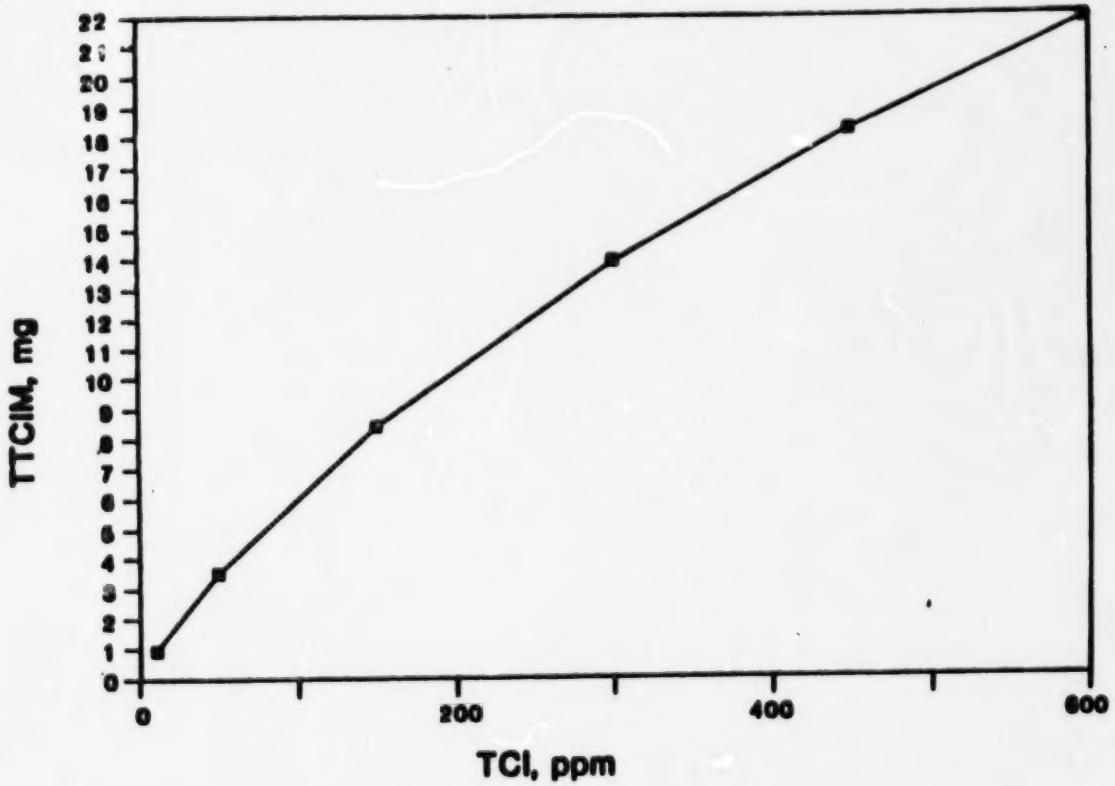

FIGURE 4-4

Relationship in the Rat Between Airborne Concentrations of TCI and Total Amount of TCI Metabolized (TTCIM mg eq) Obtained by Computer Simulation

Source: U.S. EPA, 1987b

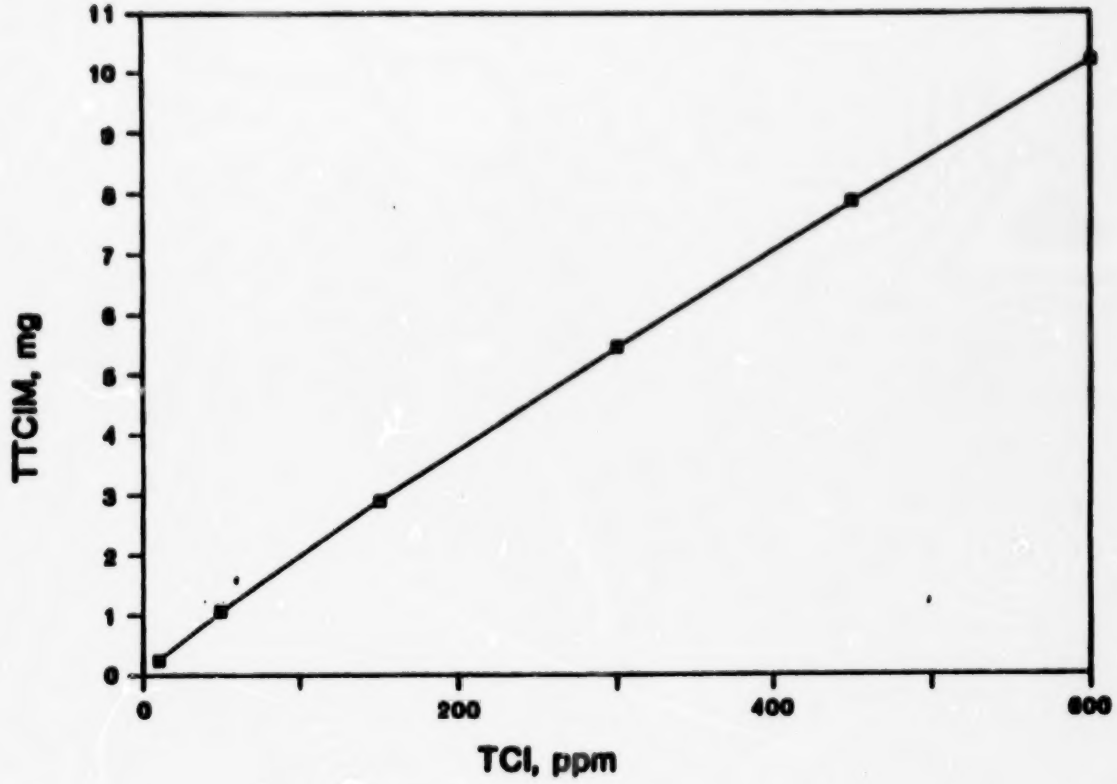

FIGURE 4-5

Relationship in the Mouse Between Airborne Concentrations of TCI and Total Amount of TCI Metabolized (TTCIM mg eq) Obtained by Computer Simulation

Source: U.S. EPA, 1987b

TABLE 4-6

Predicted Relationship Between Inhalation Exposure Level and Trichloroethylene Metabolites*

Airborne TCI Concentration (ppm)	Predicted TTCIM (mg)	
	Rat (200 g)	Mouse (30 g)
600	21.81	10.2
450	18.19	7.87
300	13.85	5.45
150	8.83	2.91
100	5.85	1.74
50	3.57	1.08
10	0.96	0.25

*Source: U.S. EPA, 1987b

4.4. WEIGHT OF EVIDENCE

Inhalation of trichloroethylene has caused pulmonary adenocarcinomas (Fukada et al., 1983); lymphomas (Henschler et al., 1980) in female mice, and hepatocellular carcinomas in both male and female mice (Bell et al., 1978) and leydig cell tumors in male rats. Oral exposure to trichloroethylene has caused hepatocellular carcinomas in both male and female mice (NCI, 1976; NTP, 1982). This constitutes sufficient evidence of carcinogenicity in animals since carcinogenicity has been demonstrated for multiple strains of mice exposed by inhalation or gavage treatment. The evidence for carcinogenicity in humans is inadequate to demonstrate or refute a carcinogenic potential. Based on EPA carcinogen risk assessment guidelines (U.S. EPA, 1986a), the overall weight of evidence for carcinogenicity of trichloroethylene was classified in Group B2 - Probable Human Carcinogen. This classification system and ranking is contained in several recent Agency analyses (U.S. EPA, 1985, 1986b,c, 1987a,b).

U.S. EPA (1987b) also noted that a metabolite of trichloroethylene, TCA, has been shown to induce liver carcinomas in male mice, thus further supporting the Group B2 classification.

5. REGULATORY STANDARDS AND CRITERIA

The current OSHA (1985) standards for occupational exposure to trichloroethylene are air concentrations of 100 ppm as an 8-hour TWA and 200 ppm as a ceiling. The acceptable maximum peak above the acceptable ceiling concentration is 300 ppm for 5 minutes in any 2 hours. Trichloroethylene is regarded as a potential carcinogen by OSHA. NIOSH has proposed an 8-hour TWA of 25 ppm for trichloroethylene (Page and Arthur, 1978). The ACGIH (1986) currently recommends a TWA-TLV of 50 ppm (270 mg/m^3) and an STEL of 200 ppm (1080 mg/m^3) for trichloroethylene.

A 10^{-5} risk level ambient water concentration of 27 µg/ℓ was derived by the U.S. EPA (1980a). This value assumes a daily intake of 2 ℓ water and 6.5 g fish and shellfish with a BCF of 10.6, and was calculated from a q_1^* of 1.26×10^{-2} $(mg/kg/day)^{-1}$ that was derived from the NCI (1976) bioassay. More recently, U.S. EPA (1986b) estimated a concentration of 2.8 µg/ℓ in drinking water associated with an excess cancer risk of 10^{-6} using the recent EPA approach, which is discussed in Chapter 6.

U.S. EPA (1985) estimated a unit risk for trichloroethylene in air of 1.3×10^{-6} $(\mu g/m^3)^{-1}$. This value is based on extrapolation from the human q_1^* of 1.3×10^{-2} (mg metabolized dose/kg/ day)$^{-1}$ which was based on the geometric mean of values derived from the NTP and NCI oral bioassays. The oral q_1^* was converted to an inhalation unit risk based on human pharmacokinetic data. U.S. EPA (1987b) has provided a unit risk estimate for inhalation of 1.7×10^{-6} $(\mu g/m^3)^{-1}$ based upon more recent inhalation data.

6. RISK ASSESSMENT

6.1. SUBCHRONIC REFERENCE DOSE (RfD_S)

Trichloroethylene is a chemical that is demonstrated to be a carcinogen in experimental animals, and data are sufficient for estimation of carcinogenic potencies by both the oral and inhalation routes. It is inappropriate, therefore, to calculate an oral or inhalation RfD_S for this chemical.

6.2. REFERENCE DOSE (RfD)

Trichloroethylene is a chemical that is demonstrated to be a carcinogen in experimental animals, and data are sufficient for estimation of carcinogenic potencies by both the oral and inhalation routes. Based upon the guidelines for this series of documents, an oral or inhalation RfD for this chemical is not calculated. It should be noted that an RfD for the noncarcinogenic effects of trichloroethylene is currently under review by the Reference Dose Workgroup of the U.S. EPA.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. U.S. EPA (1985) has estimated the 95% upper-bound estimates for hepatocellular carcinoma using the linearized multistage model of Crump and adopted by the U.S. EPA (1980b) for the data from both the NCI (1976) and NTP (1982) studies. These data are shown in Table 6-1.

Metabolized doses (see Table 6-1) were calculated from doses administered to rodents based on the data from Prout et al. (1984) using a "Michaeles-Menton" type equation, M=a x (d/b+d): d represents the experimental dose, M represents the metabolized dose and a and b are empirically determined constants. Using least-square estimates, a was determined to be 594.1 and b 702.79 (r^2=0.99) (U.S. EPA, 1985). Using the multistage model, q_1^* values were determined from animal metabolized doses. The q_1^*s in terms of human metabolized doses were estimated from the animal q_1^*s in terms of

TABLE 6-1

Incidence Rates of Hepatocellular Carcinomas in Male and Female Mice in the NTP (1982) and NCI (1976) Gavage Studies[a]

Study	Continuous Human Equivalent (animal nominal) Doses (mg/kg/day)[b]	Animal Metabolized Dose (mg/day)	Incidence Rates No. with Tumor/Total (%)
		MALE	
NTP	0 (0)	0	8/48 (17%)
	47.39[b] (1000)	31.98[c]	30/50 (60%)
NCI	0 (0)	0	1/20 (5%)
	45.11 (1169)[d]	30.90[c]	26/50 (52%)
	85.80 (2339)[d]	58.77[c]	31/48 (65%)
		FEMALE	
NTP	0 (0)	0	2/48 (4%)
	45.62 (1000)	28.17[c]	13/49 (27%)
NCI	0 (0)	0	0/20 (0%)
	31.65 (869)[d]	18.49[c]	4/50 (8%)
	61.43 (1739)[d]	35.89[c]	11/47 (23%)

[a]Source: U.S. EPA, 1985

[b]All 95% upper-limit slopes q_1^* calculated using continuous human equivalent doses.

Equivalent human dosage = animal metabolized dose x 5/7 days x l_c/L_c $(W_a/70)^{1}\}^{3}$

where W_a = weight of the mice. The average weight of males is taken as 40 g for dosed males and 35 g for dosed females for the NTP study; for the NCI study the average weights are 33 g for males and 26 g for females. L_c, the length of experiment, = 2 years and l_c, the duration of exposure, is 2 years for the NTP study and 1.5 years for the NCI study.

[c]Determined using data from Prout et al. (1984) and a "Michaeles-Menton" type equation by U.S. EPA (1985)

[d]TWA gavage dose over 78-week treatment period.

metabolized dose using a surface area approximation. Human q_1^*s in terms of exposure dosage were then back-calculated from the q_1^*s in terms of human metabolized doses (Table 6-2) (U.S. EPA, 1985).

The potency for humans, q_1^*, to be used for estimates of risk related to exposure was estimated as the geometric mean of the human administered dose q_1^*s, 1.1×10^{-2} $(mg/kg/day)^{-1}$. This value has been verified and is available on IRIS (U.S. EPA, 1987a).

6.3.2. Inhalation. U.S. EPA (1985) estimated a unit risk for trichloroethylene in air of 1.3×10^{-6} $(\mu g/m^3)^{-1}$. This value is based on extrapolation from the human q_1^* of 1.3×10^{-2} (mg metabolized dose/kg/day)$^{-1}$, which was based on the geometric mean of values derived from the NTP and NCI oral bioassays. The oral q_1^* was converted to an inhalation unit risk based on human pharmacokinetic data.

The study by Monster et al. (1976) was used for estimating the amount metabolized when a subject is exposed to 1 $\mu g/m^3$ of trichloroethylene in air.

The median amount metabolized by four subjects exposed to 70 ppm for 4 hours is 439 mg. Assuming that the dose metabolized is linearly related to the level and duration of exposure, the dose corresponding to 1 $\mu g/m^3$ of trichloroethylene in air was estimated as:

$$\text{dose/1 } \mu g/m^3 = \frac{439 \text{ mg} \times (24 \text{ hours}/4 \text{ hours})}{70 \text{ ppm} \times 5475 \text{ mg/m}^3\text{/ppm}}$$

$$= 6.9 \times 10^{-3} \text{ (mg/day)}(\mu g/m^3)^{-1}$$

$$= 6.9 \times 10^{-3}/70 \text{ kg} = 9.9 \times 10^{-5} \text{ (mg/kg/day)}^{-1}$$

Therefore, the unit risk for trichloroethylene in air is 1.3×10^{-2} (mg metabolized trichloroethylene/kg/day)$^{-1}$ x 9.9×10^{-5} (mg metabolized trichloroethylene/kg/day/$\mu g/m^3$) = 1.3×10^{-6} $(\mu g/m^3)^{-1}$ expressed in terms of ambient concentration.

TABLE 6-2

Estimated Slope Values (q_1^*) Based on Extrapolation from Data on Male and Female Mice[a,b]

Study	q_1^* (Animal) (mg metabolized dose/kg/day)$^{-1}$	q_1^* (Human) (mg metabolized dose/kg/day)$^{-1}$	q_1^* (Human) (mg administered dose/kg/day)$^{-1}$
NTP			
male mice	1.8×10^{-3}	2.2×10^{-2}	1.9×10^{-2}
female mice	7.5×10^{-4}	9.5×10^{-3}	8.0×10^{-3}
NCI			
male mice	1.6×10^{-3}[c]	2.1×10^{-2}	1.8×10^{-2}
female mice	5.0×10^{-4}[c]	6.9×10^{-3}	5.8×10^{-3}
Geometric mean	1.0×10^{-3}	1.3×10^{-2}	1.1×10^{-2}

[a]Source: U.S. EPA, 1985

[b]q_1^* is the 95% upper limit of the linear component (slope) in the multistage model. Since the dose-response curve is virtually linear below 1 mg/kg/day, the slope is numerically equal to the upper limit of the incremental lifetime risk estimates at 1 mg/kg/day.

[c]Slope is increased by $(104/90)^3$ because the duration of the experiment was less than the lifespan of the test animal.

In a more recent assessment, U.S. EPA (1987b) utilized animal inhalation bioassays to calculate a unit risk for inhalation exposure. The data sets chosen for quantitative analysis were: Leydig cell tumors in male rats (Maltoni et al., 1986); liver and lung tumors in male Swiss mice (Maltoni et al, 1986); lung tumors in female swiss mice (Maltoni et al., 1986), liver and lung tumors in female B6C3F1 mice (Maltoni et al., 1986) and lung tumors in female ICR mice (Fukada et al., 1984).

Animal metabolized doses were estimated for each experimental exposure condition utilizing the data shown in Table 4-5. Extrapolation from the doses shown in Table 4-5 to those shown in Table 6-3 involved first extrapolating to animals of different body weight by multiplying the dose from Table 4-5 by the 2/3 power of body weight. The doses were then corrected for a 7-hour vs. a 6-hour exposure by multiplying by 7/6. In addition the animal doses were converted into estimated human equivalent metabolized doses by using the ratio of the body weights to the 2/3 power. These doses were further adjusted by multiplying by the percent of the animals lifetime that the experimental time period represented. An animal lifetime of 28 months was assumed for this calculation. As a result, the human HEDs in Table 6-3 derived from studies using Swiss and B6C3F1 mice were multiplied by 0.133 to account for 78 weeks of exposure, 5 days/week, 7 hours/day and the HEDs derived from the study using ICR mice (107-week exposure) were multiplied by 0.183.

Similarly, the data for metabolized dose and human equivalent dose for Sprague-Dawley rats are shown in Table 6-4. For this 104-week study, exposure time adjusted doses could be calculated by multiplying by 0.178.

The U.S. EPA (1987b) then calculated slope estimates (q_1^*) utilizing the multistage model for each of these data sets. Slope estimates were

TABLE 6-3

Summary of Estimated Metabolized Dose from the Animal Bioassays, Corresponding Human Equivalent Dose (HED) and Tumor Incidence for the Mouse Bioassays*

Trichloroethylene Exposure	Metabolized Dose (mg)		Lung Tumor Incidence	Liver Tumor Incidence	Reference
	Animal	HED			
Swiss Mice, Male (47 grams)					
600	16.1	2148	27/90	13/90	Maltoni et al., 1986
300	8.59	1148	23/89	8/89	
100	2.74	367	11/89	2/89	
0			10/89	4/88	
Swiss Mice, Male (40 grams)					
600	14.4	2148	20/89		Maltoni et al., 1986
300	7.71	1148	13/90		
100	2.46	367	15/89		
0			15/90		
B6C3F1 Mice, Female (32 grams)					
600	12.4	2148	14/87	9/89	Maltoni et al., 1986
300	6.64	1148	7/89	4/89	
100	2.12	367	6/90	4/90	
0			6/90	3/90	
ICR Mice, Female (40 grams)					
450			11.46		Fukada et al., 1983
150	11.1	1658	13/50		
50	4.12	613	5/50		
0	1.53	227	6/49		

*Source: Adapted from U.S. EPA, 1987b

TABLE 6-4

Summary of Estimated Metabolized Dose from the Rat Bioassay, Corresponding Human Equivalent Dose (HED)and Tumor Incidence*

Trichloroethylene Exposure	Metabolized Dose (mg)		Leydig Cell Tumor Incidence	Reference
	Animal	HED		
600	52.0	1289	31/129	Fukada et al., 1983
300	33.0	818	30/130	
100	13.9	346	16/130	
0			6/135	

*Source: Adapted from U.S. EPA, 1987b

calculated both by using body weight as the scaling factor and by using estimated surface area ($(weight)^{2/3}$) as the scaling factor. The estimates seemed to be in closer agreement when a surface area assumption was utilized. These data are shown in Table 6-5. The slope estimates are all in the same range as that calculated by U.S. EPA (1985), 1.3×10^{-2}, based upon mouse gavage studies.

The geometric means of the mouse potency estimates were 8.7×10^{-3} and 1.7×10^{-2} $(mg/kg/day)^{-1}$ for the liver and lung, respectively. The higher of the two values was chosen for use in subsequent extrapolations. This value was chosen over that based upon the Leydig cell tumors in male rats for several reasons: the fact that it reflects a first pass effect resulting from inhalation and because it is based on a response seen in multiple mouse strains and in both sexes (U.S. EPA, 1987b).

This q_1^* was then converted into a unit risk for inhalation exposure by utilizing the same data base described in Section 6.3.2. where it was estimated that exposure of humans to air containing 1 $\mu g/m^3$ should result in a metabolized dose of 1×10^{-4} mg metabolized trichloroethylene/kg/day. Therefore the unit risk for inhalation exposure to trichloroethylene was calculated as follows:

$$[1.7 \times 10^{-2} (mg\ metabolized/kg/day)^{-1}] \times [1 \times 10^{-4}\ mg\ metabolized/kg/day/\mu g/m^3]$$

$$= 1.7 \times 10^{-6}\ (\mu g/m^3)^{-1}$$

TABLE 6-5

Human q_1^* Estimates per (mg metabolized dose/kg/day)*

Data	q_1^*
Male Rats	
Leydig cell	2.7×10^{-2}
Swiss Male Mice	
Liver	1.1×10^{-2}
Lung	2.4×10^{-2}
Swiss Female Mice	
Lung	9×10^{-3}
B6C3F1 Female Mice	
Liver	7.1×10^{-3}
Lung	1.3×10^{-2}
ICR Female Mice	
Lung	2×10^{-3}

*Source: Adapted from U.S. EPA, 1987b

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APPENDIX

Summary Table for Trichloroethylene Using the Mouse

Carcinogenic Potency	Experimental Dose/Exposure	Effect	q_1^* or Unit Risk Slope	Reference
Inhalation	50-200 ppm	lung tumors	$1.7 \times 10^{-6}(\mu g/m^3)^{-1}$*	Fukada et al., 1983; Maltoni et al., 1986; U.S. EPA, 1987b
Oral	1169-2339 mg/kg/day	hepatocellular carcinoma	$1.1 \times 10^{-2}(mg/kg/day)^{-1}$	NCI, 1976; NTP, 1982; U.S. EPA, 1985

*For purposes of comparison with earlier HEAs, this value may be converted to $6 \times 10^{-3}(mg/kg/day)^{-1}$ by assuming a human inhalation volume of 20 m^3 and a body weight of 70 kg. This reflects a simple unit transformation and does not include an absorption estimate.

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